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Outcomes of Surgical Resection of Pancreatic Cystic Neoplasms Based on the European Expert Consensus Statement: A Prospective Observational Study

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ABSTRACT

Background: The most common types of true epithelial exocrine pancreatic cystic neoplasms are serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs), intra-ductal papillary mucinous neoplasms (IPMNs), and solid pseudo-papillary neoplasms (SPPNs). Both open and laparoscopic pancreatic surgeries are major procedures with significant morbidity and mortality rates. This study aimed to determine the outcomes of laparoscopic pancreatic surgery in managing true exocrine epithelial pancreatic cystic neoplasms in terms of postoperative pancreatic fistula and recurrence rate and to identify associated risk factors.

Methods: A prospective observational single-center study between June 2014 and January 2018 included 63 patients with true exocrine epithelial pancreatic cystic neoplasms. Distal pancreatectomy (Laparoscopic and open approaches) and pancreaticoduodenectomy (open approach) were performed according to the tumor site.

Results: Pancreatic fistula developed in 10 cases (10/63, 16%), most commonly after surgical resection in MCNs (3 cases) and SPPNs (3 cases), while grade C (according to the International Study Group on Pancreatic Fistula, ISPGF) was more common in IPMNs (one case) and SPPNs (one case). Most cases of fistula (8 patients) followed distal pancreatectomy. Recurrence occurred in 6 cases (9.5%), mostly following resection of MCN (3 patients), and recurrence commonly occurred at the resection margin. Predictive factors of pancreatic fistula were symptoms ($p = 0.006$) and disease located at the pancreatic tail ($p = 0.02$) (RR 3.15, 95%CI 1.51-6.73). Predictors of recurrence were symptoms ($p=0.02$) (RR 1.9, 95%CI 1.45-2.45), location at the head ($p=0.01$) (RR 3.3, 95% CI 1.9-6.3), elevated CA19-9 ($p=0.014$) (RR 2.5, 95%CI 1.8-3.95) and pancreatic duct < 5 mm ($p=0.000006$) (RR 5.9 , 95%CI 2.8-12.3). The survival rate at 2.5 years was 96.7%, 100%, 88.9%, and 80% for SCNs, MCNs, IPMNs, and SPPNs, respectively.

Conclusion: Surgical surgery to treat true exocrine epithelial pancreatic cystic neoplasms seems safe and effective. Pancreatic fistula and recurrence occurred in 16% and 9.5% of patients, respectively. Most cases followed MCN resection.

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Key words: exocrine tumor, fistula, laparoscopy, pancreatic cyst, pancreatectomy, pancreatic neoplasms

INTRODUCTION

Pancreatic cystic neoplasms (PCN) are observed in approximately 2-45% of the population (1). PCNs are almost present in 10-15% of overall pancreatic cysts and in 1% of all pancreatic tumors. According to the World Health Organization (WHO), there are four main types of true exocrine epithelial PCNs: serous cystic neoplasm (SCN), mucinous cystic neoplasm (MCN), intra-ductal papillary mucinous neoplasms (IPMNs), and solid pseudo-papillary neoplasm (SPPNs). SPPNs are less common and rarer than IPMNs, SCNs, and MCNs (2).

True exocrine epithelial PCNs represent a wide range of biological behaviour that varies from benign to malignant. Accordingly, proper differential diagnosis and surgical excision of true exocrine epithelial PCN may prevent the advancement towards invasive pancreatic adenocarcinoma (3). The differentiation between the various types of PCN is often challenging (4). Computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) - guided cytology are used as diagnostic tools to assist in the evaluation of resectability, pancreatic duct communication, and the identification of pancreatic ductal dilatation (5).

In recent years, there has been technical improvement in laparoscopic surgery of the pancreas. In some high-volume centres (6), laparoscopic pancreaticoduodenectomy (LPD) has seen an acceptance surge since 2010. However, many centres still do not advocate LPD as a standard procedure for fear of a higher complication rate. Indeed, a multicenter study showed severe complications in 49.66% of the patients, whereas 6.51% experienced grade B or C postoperative pancreatic fistula (POPF). In addition, the 30- and 90-day mortality rates were 2.43% and 5.93%, respectively (7).

A systematic review including 773 patients stated no recurrence after resection of MCN and did not require lifelong follow-up (8). Patients with surgically resected MCNs with invasive cancer have a 25% risk of cancer recurrence (9). Follow-up for IPMNs after surgery should continue for life (10).

A European expert consensus statement on PCNs was produced in 2013 by the European Study Group on Cystic Tumours of the Pancreas, United European Gastroenterology (UEG), and the European Pancreatic Club (EPC) (11). To improve the diagnosis and management of all types of PCNs, the earlier consensus was superseded in 2016 by European evidence-based guidelines (5).

The primary aim of our study is to assess the incidence of pancreatic fistula and the recurrence rate of the disease following surgical resection of true exocrine epithelial pancreatic cystic neoplasms. The secondary objective is identifying risk factors for post-operative pancreatic fistula and recurrence.

PATIENTS AND METHODS

Study design and participants

This is a single-center observational study with prospectively collected data designed to present our experience with 63 patients who underwent surgery for true epithelial exocrine PCN in Zagazig university hospital between June 2014 and January 2018. Patients eligible for the study included any age, sex, and a tumour of any size, with a diagnosis of true epithelial exocrine pancreatic cystic neoplasms and in accordance with at least one of the following criteria from the international consensus guidelines for resection (11). These criteria include SCN (symptomatic cases or suspicious cases after meticulous preoperative investigation), MCN (all patients fit for surgery), and IPMN (main duct-mixed duct-branch duct). Absolute indications included jaundice, diabetes, acute pancreatitis, wall nodule, main pancreatic duct (MPD) > 6 mm and size ≥4 cm. Relative indications were the rapid increase in size, the increase in CA 19-9, and all cases of SPPNs. Patients excluded from the study were those with endocrine pancreatic tumors, solid pancreatic tumors, previous pancreatic surgery, recurrent pancreatic tumors, combined operations, prior history of malignancy, and misdiagnosed cases that were discovered on the post-operative pathologic examination of the surgical specimen. Sixty-three patients analyzed in the study were categorized into four groups: Group A (30 patients) that were diagnosed as SCNs; Group B (19 patients) that were diagnosed as MCNs; Group C (9 patients) that were diagnosed as IPMNs, and Group D (5 patients) that were diagnosed as SPPNs.

Definitions and measurement of outcomes

The pancreatic fistula was defined, diagnosed, and

treated according to the recommendations of the International Study Group on Pancreatic Fistula (ISGPF), released in 2005 (and revised in 2016), as an amylase level in the fluid collected from the drain on the third postoperative day (POD) greater than three times the serum amylase level. POPF was classified into one of three grades - biochemical leak (previously called grade A), grade B, or grade C. The amylase level in the drain fluid on POD 3 was measured in all patients. (12). Recurrence of the pancreatic tumour was defined as convincing radiographic evidence of relapse of the disease during follow-up after pancreatic tumour resection and with histologic confirmation when possible. The recurrence sites were classified as pancreatic remnant recurrence or extrapancreatic relapse (13). The cystic fluid carcinoembryonic antigen (CEA) cutoff level of 192 ng/ml with a sensitivity of 73% and specificity of 84% using the IMX-MEIA, Abbott method was suggestive of PCN diagnosis. The cyst fluid amylase cutoff is 250 IU/l using the Roche Diagnostic Modular System (Roche Diagnostics Corporation, Indianapolis, IN) (14). All postoperative complications were graded according to the Clavien–Dindo classification (15).

Perioperative techniques

Preoperative work-up was assessed by a routine multidisciplinary board that included pancreatic surgeons, anesthesiologists, radiologists, and medical oncologists. The diagnosis was based on CT or MRI of the abdomen and endoscopic ultrasound with biopsy and cytology for all cases. One ampicillin-sulbactam 2 g IV was given as a prophylaxis to the patients one hour before the surgical incision, and the dose was repeated every four hours. For penicillin allergy, ciprofloxacin 400 mg IV was given. Antibiotics were administered during the first three days following surgery and may have been extended if there was evidence of infection based on culture and sensitivity. Thrombotic prophylaxis with subcutaneous enoxaparin 4000 IU was administered 12 hours postoperatively.

During the study, all procedures were performed by experienced hepato-biliary and pancreatic surgeons. In pancreatic head neoplasms, the standard procedure was pancreaticoduodenectomy with or without pylorus-preserving with hepaticojejunostomy, gastrojejunostomy, and pancreaticojejunostomy (16). Neoplasms in the body and tail were treated with a distal pancreatectomy with or without a splenectomy (17).

One drain was put in the pelvis, and two drains were put at the peri-anastomotic site and maintained in situ as long as discharge came out. We recorded all drain outputs daily for seven days. Amylase levels were obtained from drains near the pancreatic remnant anastomosis. All drains were removed when the amylase concentration was below three times the normal serum levels. CT was used to assess fluid collections with CT-guided drainage performed upon indications. Follow-up schedules were one, three, six, 12, 24, and 30 months after hospital discharge with median follow up period 55±12.5 months. Patients were contacted by phone, follow-up visits at the outpatient clinic, or e-mail messages. Follow-up included a complete history and clinical examination and performing a CT after six months (to detect recurrence). CT-guided biopsy with histopathological examination confirmed disease recurrence. For patients who developed abdominal symptoms or for surveillance in the follow-up period, CT was indicated. The intervals between the surgery date and the diagnostic imaging evidence of recurrence were documented. No cases were missed during the follow-up period.

Statistical analysis

Data collected was entered and analysed using the Microsoft Excel software and then imported into the Statistical Package for the Social Sciences (SPSS) version 20.0 software for analysis. According to the data type, qualitative data was represented as numbers and percentages, and quantitative data was represented by mean ± SD. Quantitative data conforms to a normal distribution. The following tests were used to test differences for significance, difference, and qualitative variable association by the Chi-square test (X2). Differences between quantitative independent groups by t-test or Mann Whitney, paired by paired t or sign, multiple by ANOVA or Kruskal-Wallis, independent predictors by logistic regression and ROC curve for cutoff. Using a Kaplan-Meier analysis to estimate overall survival and recurrence-free survival, using the independent t-test or the Mann-Whitney U test for normally and non-normally distributed quantitative variables, respectively. A significant P-value was set at <0.05 and <0.001 for highly significant results.

RESULTS

Figure 1 shows the flow diagram of inclusion and exclusion patients.

Demographic data of the studied groups

Most of the studied groups were between 30 and 50

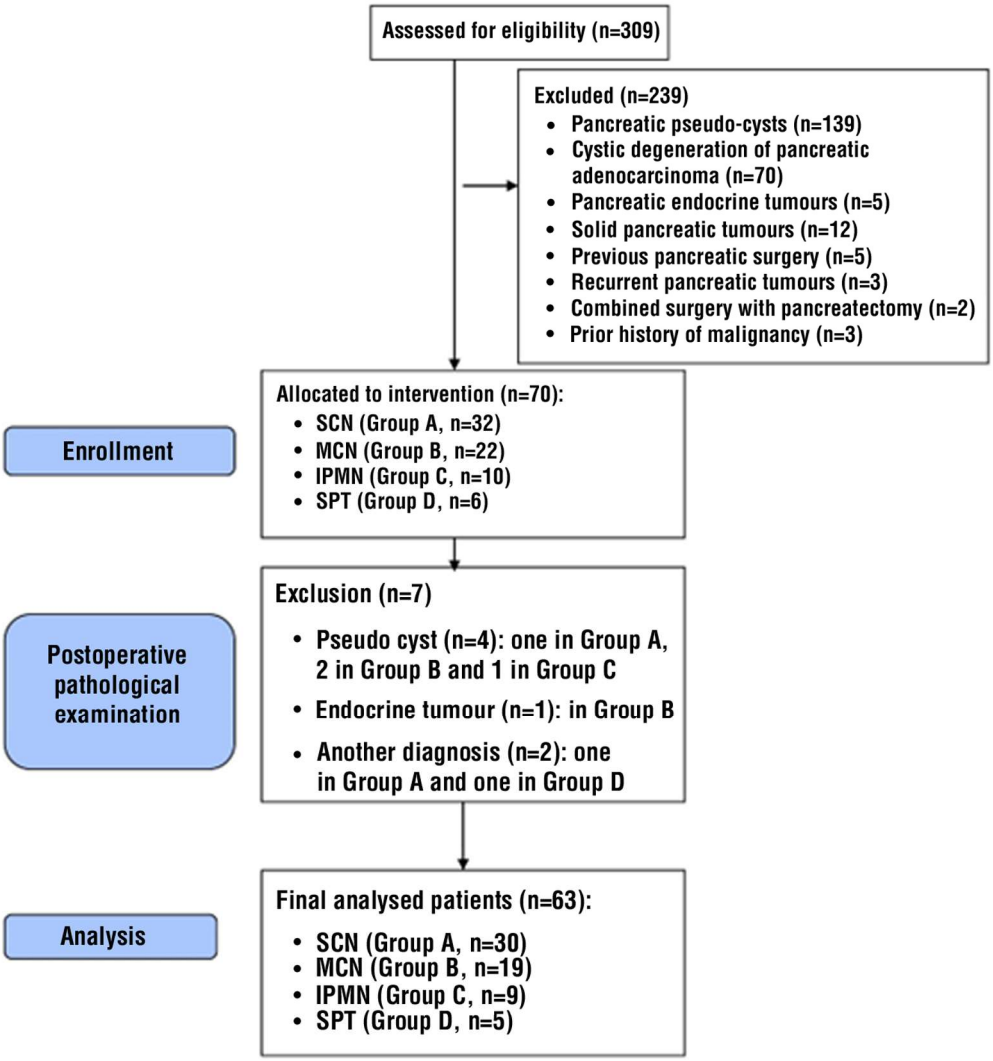


Figure 1 - Flow diagram of inclusion and exclusion patients

years old (28 patients, 44.5%), with female predominance (41 patients, 65%). The commonest presentation was epigastric pain(6 patients, 9.5%), while asymptomatic cases discovered accidentally represented 38% of cases (24 patients). DM was present in 20.6% of cases (13 patients), with a mean BMI of 32.7±2.95. Most cases were diagnosed as benign cysts (51 patients, 81%) preoperatively. Low levels of cystic fluid CEA, amylase, and CA 19-9 were present in 35 patients (55.5%), 46 patients (73%) and 35 patients (55.5%), respectively. CT of the cysts showed solitary cyst in 48 patients(76%) of cases, multilocular in 42 patients(66%), absent solid component (47 patients,75%), absent mural nodule (51 patients,81%), large cyst size ≥ 3cm (50 patients,79.4%), pancreatic duct diameter ≥5mm (50 patients,79.4%). The commonest site of the tumour was in the body (28 patients, 44%), followed by the head (19 patients, 30%) and tail (16 patients, 26%). cyst connected to pancreatic duct in 14% of cases only(9 patients) (*table 1*).

Primary outcomes

Distal pancreatectomy with splenic preservation was the most common procedure (29 patients, 46.2%) with a mean operative time of 152.7±0.5 minutes. The commonest operation performed in SCN, MCN, and SPPNs was distal pancreatectomy with splenic preservation while pylorus preserving pancreaticoduodenectomy was the commonest operation done for IPMNs. A pancreatic fistula developed in 10 cases (10/63, 16%), mostly clinically relevant pancreatic fistula (7/10) mostly Grade B(5/10). As regards the incidence of fistula, the most common surgery following fistula was surgery for MCN and SPPN. As

Table 1 - Demographic data and preoperative clinical data

	All patients (n= 63)	Group A (n=30)	Group B (n=19)	Group C (n=9)	Group D (n=5)	P
Age						
< 30 years	10(16%)	3(10%)	3(15.8%)	1(11.1%)	3(60%)	0.009*
30-50 years	28(44.5%)	12(40%)	13(68.4%)	2(22.2%)	1(20%)	
>50 years	25(39.5%)	15(50%	3(15.8%)	6(66.7%)	1(20%)	
Sex						
Male	22(35%)	8(26.6%)	6(31.6%)	7(77.8%)	1(20%)	0.03*
Female	41(65%)	22(73.4%)	13(68.4%)	2(22.2%)	4(80%)	
c/p						
asymptomatic(incidental finding± suspected	24(38%)	17(56.7%)	4(21%)	2(22.2%)	1(20%)	
malignancy or doubtful diagnosis)	8(12.6%)	3(10%)	3(15.8%)	1(11.1%)	1(20%)	
palpable mass	31(49%)	13(43.3%)	9(47.4%)	6(66.7%)	3(60%)	0.57
Epigastric pain	15(24%)	4(13.3%)	7(36.8%)	2(22.2%)	2(40%)	
Nausea /vomiting	6(9.5%)	3(10%)	1(5.3%)	1(11.1%)	1(20%)	
weight loss jaundice	6(9.5%)	1(0.3%)	2(10.6%)	2(22.2%)	1(20%)	
Diabetes mellitus	13(20.6%)	6(20%)	3(15.8%)	3(33.3%)	1(20%)	0.26
BMI(kg/m^2) (mean ± SD)			32.7 ± 2.95			
Diagnosis						
Benign	51(81%)	27(90%)	16(84.2%)	4(44.4%)	4(80%)	0.02*
Malignant	12(19%)	3(10%)	3(15.8%)	5(55.6%)	1(20%)	
fluid chemistry						
1- CEA						
Elevated	28(44.5%)	4(13.3%)	15(79%)	8(88.9%)	1(20%)	0.00**
Low	35(55.5%)	26(86.7%)	4(21%)	1(11.1%)	4(80%)	
2-amylase						
Elevated	17(27%)	6(20%)	3(15.8%)	7(77.8%)	1(20%)	0.003*
Low	46(73%)	24(80%)	16(84.2%)	2(22.2%)	4(80%)	
3-CA 19-9						
Elevated	28(44.5%)	4(13.3%)	15(79%)	8(88.9%)	1(20%)	0.00**
low	35(55.5%)	26(86.7%)	4(21%)	1(11.1%)	4(80%)	
CT findings of cystic neoplasm						
1-number of cyst						
Solitary	48(76%)	26(86.7%)	16(84.2%)	2(22.2%)	4(80%)	0.0007**
Multiple	15(24%)	4(13.3%)	3(15.8%)	7(77.8%)	1(20%)	
2-number of loculi						
Unilocular	21(33.5%)	14(46.6%)	2(10.6%)	2(22.2%)	3(60%)	0.03*
Multilocular	42(66.5%)	16(53.4%)	17(89.4%)	7(77.8%)	2(40%)	
3-solid component						
Yes	16(25%)	3(10%)	4(21%)	5(55.6%)	4(80%)	0.001**
No	47(75%)	27(90%)	15(79%)	4(44.4%)	1(20%)	
4-mural nodule						
Yes	12(19%)	3(10%)	3(15.8%)	5(55.6%)	1(20%)	0.023*
No	51(81%)	27(90%)	16(84.2%)	4(44.4%)	4(80%)	
5-size of cyst in largest diameter in cm(CT)						
< 3 cm	13(20.6%)	6(20%)	3(15.8%)	3(33.3%)	1(20%)	0.76
≥ 3 cm	50(79.4%)	24(80%)	16(84.2%)	6(66.7%)	4(80%)	
6-Pancreatic duct diameter in mm(CT)						
< 5 mm	13(20.6%)	8(26.6%)	3(15.8%)	1(11.1%)	1(20%)	0.69
≥ 5 mm	50(79.4%)	22(73.4%)	16(84.2%)	8(88.9%)	4(80%)	
7-site of cyst in pancreas (CT)						
Head	19(30%)	8(26.6%)	3(15.8%)	7(77.8%)	1(20%)	0.002*
Body	28(44%)	10(33.5%)	14(73.6%)	1(11.1%)	3(60%)	
Tail	16(26%)	12(39.9%)	2(10.6%)	1(11.1%)	1(20%)	
Connection to duct(MRI finding)						
Yes	9(14%)	0(0%)	1(5.3%)	8(88.9%)	0(0.00%)	0.00**
No	54(86%)	30(100%)	18(94.7%)	1(11.1%)	5(100%)	

P value:*≤0.05: Statistically significant, **≤0.001: Highly statistical significant.
Group A (serous cystic neoplasms), Group B (mucinous cystic neoplasms), Group C (intra-ductal papillary mucinous neoplasms), and Group D (solid pseudo-papillary neoplasms).
ASA: American Society of Anesthesiologists. CEA: carcinoembryonic antigen. CA 19-9: Cancer Antigen 19-9. EUS:Endoscopic ultrasound
CT: Computerized Tomography. MRI:Magnetic resonance imaging. BMI: Body Mass Index

regard severity of fistula, biochemical leak occurred in 3 cases (3/10) while clinically relevant fistula occurred in 7 cases (7/10). Clinically relevant fistulas commonly follow surgery for MCN, IPMN, and SPPN. As regards the origin of the fistula, most cases followed distal pancreatectomy (8/10), while 2 cases(2/10) followed pancreaticoduodenectomy. Recurrent tumour after surgical resection occurred in 6 cases with MCN resection was the commonest surgery to be followed by recurrence (3/6).Recurrent tumour commonly occurred at resection margin (4/6) then liver (2/6) with no intraperitoneal recurrence. Reoperation was performed in 4 cases (4/6) with overall survival at 2.5 years of 96.7%, 100%, 88.9%, and 80% in groups SCN, MCN, IPMN, and SPPN, respectively (*table 2*).

Accuracy, sensitivity, and specificity of imaging studies regarding the preoperative and postoperative diagnosis

An abdominal CT, MRI, and endoscopic ultrasound with FNAC were performed on all patients during the preoperative work-up. In group A, 3 cases had a preoperative diagnosis of malignancy, but two of these cases were confirmed as benign in the postoperative histopathology with a sensitivity of 50.0%, specificity of 88.8%, positive predictive value of 100.0%, negative predictive value of 88.8%, and accuracy of 90.0%. In group B, 2 cases (2/16) were diagnosed preoperatively as benign but were discovered to be malignant in the postoperative histopathology with a sensitivity of

Table 2 - Intraoperative and postoperative outcomes

	All patients (n=63)	Group A (n=30)	Group B (n=19)	Group C (n=9)	Group D (n=5)	P
Intraoperative data						
Types of surgery						
1 - pancreatico-duodenectomy(open)						
• Pylorus preserving pancreatico-duodenectomy	13(20.6%)	6(20%)	2(10.6%)	4(44.4%)	1(20%)	0.051
• Pancreaticoduodenectomy without pylorus preserving	6(9.5%)	2(6.7%)	1(5.3%)	3(33.3%)	0(0.00%)	
2 - distal pancreatectomy (lap and open)						
• Distal pancreatectomy with splenic preservation	29(46.2%)	18(60%)	8(42.4%)	0(0.00%)	3(60%)	
• Distal pancreatectomy with splenectomy	13(20.6%)	4(13.4%)	7(36.7%)	1(11.1%)	1(20%)	
3 -open Bypass surgery (hepaticojejunostomy and gastrojejunostomy)	2(3%)	0(0.00%)	1(5.3%)	1(11.1%)	0(0.00%)	
Operative time (mean±SD)						
• Pylorus preserving pancreatico-duodenectomy	185.3±7.5	186.2±20.0	191.2±25.0	176.2±13.0	187.9±30	0.41
• Pancreatico-duodenectomy without pylorus preserving	176.1±0.5	172.5±193.0	183.5±18.0	169.5±26.0	179.1±28.0	0.064
• Distal pancreatectomy with splenic preservation	152.7±0.5	150±6.0	157±23.0	144±16. 0	160±22.80	0.09
• Distal pancreatectomy with splenectomy	210.2±0.5	209±17.0	220±11.0	200±11.0	212±16.30	0.069
• Biopsy,cholecystectomy and Bypass surgery (hepaticojejunostomy and gastrojejunostomy)	119.2±0.5	116±14.0	122±17.0	120±10.0	119±13.0	0.189
Postoperative outcomes						
Pancreatic fistula						
• ISPGF grade A(biochemical leak)	10(16%)	2(6.7%)	3(15.8%)	2(22.2%)	3(60%)	0.75
• clinically-relevant pancreatic fistula	3(4.7%)	1(3.3%)	1(5.3%)	0	1(20%)	
1. ISPGF grade B	5(8%)	1(3.3%)	2(10.6%)	1(11.1%)	1(20%)	
2. ISPGF grade C	2(3%)	0%	0%	1(11.1%)	1(20%)	
Site of the fistula						
• Following distal pancreatectomy	8(13%)	2(6.7%)	2(10.6%)	2(22.2%)	2(40%)	0.02*
• Following pancreaticoduodenectomy	2(3%)	0%	1(5.3%)	0%	1(20%)	
Recurrence	6(9.5%)	1(3.3%)	3(15.8%)	1(11.1%)	1(20%)	0.38
Site of recurrence						
Resection margin	4(6%)	1(3.3%)	2(10.6%)	1(11.1%)	0	
Liver	2(3%)	0	1(5.3%)	0	1(20%)	0.45
Intra-peritoneal	0	0	0	0	0	
Reoperation for recurrence	4(6%)	1(3.3%)	1(5.3%)	1(11.1%)	1(20%)	0.20
Overall survival, % at 2.5 y	57(90.5%)	29(96.7%)	16(84.2%)	8(88.9%)	4(80%)	0.41

P value:* ≤ 0.05: Statistically significant, ** ≤ 0.001: Highly statistical significant.
Group A (serous cystic neoplasms), Group B (mucinous cystic neoplasms), Group C (intra-ductal papillary mucinous neoplasms), and Group D (solid pseudo-papillary neoplasms).
Lap: Laparoscopic, ICU: Intensive Care Unit, ISPGF: International Study Group on Pancreatic Fistula

Table 3 - Accuracy, sensitivity and specificity of imaging studies as regard preoperative and postoperative diagnosis

	All patients (n=63)	Group A (n=30)	Group B (n=19)	Group C (n=9)	Group D (n=5)
Preoperative diagnosis (CT,MRI,cyst analysis)					
Benign	50(79.4%)	27(90%)	16(84.2%)	4(44.4%)	3(60%)
Malignant	13(20.6%)	3(10%)	3(15.8%)	5(55.6%)	2(40%)
Postoperative diagnosis (based on HPE)					
Benign	49(77.7%)	29(96.5%)	14(73.6%)	3(33.3%)	3(60%)
Malignant	14(22.3%)	1(3.5%)	5(26.4%)	6(66.7%)	2(40%)
Sensitivity		50.0%	40.0%	66.7%	50.0%
Specificity		88.8%	92.8%	66.7%	66.7%
+VE Predictive value		100.0%	66.7%	80.0%	50.0%
-VE Predictive value		88.8%	92.8%	66.7%	66.7%
Accuracy		90.0%	50.0%	66.7%	60.0%

Group A (serous cystic neoplasms), Group B (mucinous cystic neoplasms), Group C (intra-ductal papillary mucinous neoplasms), and Group D (solid pseudo-papillary neoplasms).
CT: Computerized Tomography, MRI: Magnetic resonance imaging, HPE: Histopathological Examination

40.0%, specificity of 92.8%, a positive predictive value of 66.7%, a negative predictive value of 92.8%, and an accuracy of 50.0%. In group c, one case (1/4) that was considered preoperatively as benign turned out to be malignant in the postoperative histopathology with a sensitivity of 66.7%, specificity of 66.7%, positive predictive value of 80.0%, negative predictive value of 66.7%, and accuracy of 66.7%. In group D, there was no misdiagnosis between the preoperative and the post-operative work-up, with a sensitivity of 50.0%, specificity of 66.7%, positive predictive value of 50.0%, negative predictive value of 66.7%, and accuracy of 60.0% (*table 3*).

Secondary outcomes

Univariate analysis of predictive factors for post-operative pancreatic fistula showed that the factors most predictive for pancreatic fistula were symptomatic disease (p = 0.006) and disease location at the tail of the pancreas (p = 0.02) (RR 3.15, 95%CI 1.51-6.73) (*table 4*).

Univariate analysis of predictive factors for recurrence showed that predictive for recurrence were symptomatic disease (p = 0.02) (RR 1.9, 95%CI 1.45-2.45) , disease location at the pancreatic head (p = 0.01) (RR 3.3, 95%CI 1.9-6.3) , elevated CA19-9 (p = 0.014) (RR 2.5 , 95%CI 1.8-3.95) and pancreatic duct diameter <5mm (p = 0.000006) (RR 5.9, 95%CI 2.8-12.3) were significantly associated with recurrence (*table 5*).

The multi-variable analysis did not reveal any significant independent predictors for recurrence (*table 6*).

DISCUSSION

So far, few studies have explicitly dealt with the postoperative outcome after resectioning rare true exocrine pancreatic tumors. The current prospective

Table 4 - Univariate analysis of predictive factors of pancreatic fistula

	Fistula (n=10)	No fistula (n=53)	P
Age, years, median	49.52±12.36	46.95±14.36	0.385
Gender			
Male	4 (40.0%)	18(33.9%)	0.61
Female	6(60.0%)	35(66.1%)	
Symptoms			
Yes	10(100.0%)	29 (54.7%)	7.31
No	0(0.00%)	24 (45.3%)	
Tumor location (number)			
Head	2(20. 0%)	17(32.0%)	0.02*
Body	2(20. 0%)	26(49.0%)	
Tail	6(60.0%)	10(19.0%)	
Cyst fluid amylase or CEA			0.75
Elevated	4(40.0%)	24(45.3%)	
Low	6(60.0%)	29(54.7%)	
CA19-9			0.289
Elevated	6(60.0%)	22(41.5%)	
Low	4(40.0%)	31(58.5%)	
Tumor size (cm)			0.42
< 3 cm	3(30.0%)	10(19.0%)	
≥ 3 cm	7(70.0%)	43(81.0%)	
Pancreatic duct diameter			0.09
< 5 mm	4(40.0%)	9 (16.9%)	
≥ 5 mm	6(60.0%)	44(70.1%)	
Site of the fistula			0.02*
Following distal pancreatectomy	8(80%)	34(64%)	
Following pancreaticoduodenectomy	2(20%)	17(32%)	

P value:*≤ 0.05: Statistically significant. CEA: Carcinoembryonic Antigen
CA19-9:Cancer Antigen 19-9

Table 5 - Univariate analysis of predictive factors of recurrence

	Recurrence (n=6)	No recurrence (n=57)	P	RR (CI 95%)
Age, years, median	53.52±13.65	48.95±15.23	0.18	
Gender				
Male	4(66.7%)	18(23.3%)	0.08	
Female	2(33.3%)	39(73.4%)		
Symptoms				
Yes	6(100.0%)	30(52.6%)	0.02*	
No	0(0.00%)	27(47.4%)		1.9 (1.45-2.45)*
Tumor location (number)				
Head	5(83.3%)	14(24.5%)	0.01*	3.3 (1.9 -6.3)*
Body	1(16.7%)	27(47.3%)		
Tail	0(0.00%)	16(28.7%)		
Cyst fluid amylase or (CEA)				
Elevated	4(66.7%)	24(42.1%)	0.24	
Low	2(33.3%)	33(57.9%)		
CA19-9				
Elevated	6(100.0%)	22(38.5%)	0.014*	2.5 (1.8-3.95)*
Low	0(0.00%)	35(61.5%)		
Pancreatic tumor size (centimeters)				
< 3 cm	3(50.0%)	10(17.5%)		
≥ 3 cm	3(50.0%)	47 (82.5%)	0.06	
Pancreatic duct diameter				
< 5 mm	5(83.3%)	8(14.0%)	0.000006**	5.9 (2.8-12.3)*
≥ 5 mm	1(16.7%)	49(86.0%)		

P value:* ≤ 0.05: Statistically significant, ** ≤ 0.001: Highly statistical significant.
CEA: Carcinoembryonic Antigen, CA19-9:Cancer Antigen 19-9

observational study, which was conducted on 63 patients, provides further evidence concerning the postoperative complications of open and minimally-invasive surgery of PCNs with a particular interest in the documentation of postoperative pancreatic fistula and disease recurrence. There are challenges between patients' exposure to surgery with all its complications and the high incidence of benign tumors. We found that pancreatic fistula developed in 10 patients (16%), with a grade B severity in half of them. Recurrence occurred in 6 patients (9.5%), with half of the recurrences occurring after resectioning mucinous cystic neoplasms.

In a previous study, Bassi et al. stated that post-operative pancreatic fistula incidence ranges between 1% and 36% (12). Eshmuminov D et al. conducted a systematic review and meta-analysis of 122 studies and found that the total postoperative pancreatic fistula rate (pooled grade B and C) after pancreatoduodenectomy was 14.5%, whereas it was 15.5% after distal pancreatectomy. In pancreatoduodenectomy, the post-operative pancreatic fistula rate was higher when the pancreatic consistency was softer (18). Furthermore, Pratt W et al., in their study on 256 patients and following the ISGP recommendations of 2005, compared the incidence of pancreatic fistula after proximal pancreatectomy, distal pancreatectomy, and central pancreatectomy. They revealed that fistula of any extent (A-C) occurred in one-third of the patients (32.4%), with 6% of readmission, 2% of reoperation, and no mortality. The overall incidence of the fistula was similar after proximal and distal pancreatectomy (30% vs. 33%; p = 0.61), and the overall incidence and severity of the fistula after central pancreatectomy was high (19).

Table 6 - Logestic regression for independent predictors for recurrence

Factor	Wald	P	OR (CI 95%)
Symptom	1.524	0.254	2.32 (0.85-5.63)
Tumour in pancreatic head	1.585	0.214	2.63 (0.74-11.32)
Elevated CA19-9	1.874	0.185	3.63 (0.94-13.52)
Pancreatic duct <5mm	2.158	0.068	2.88 (0.93-7.55)

In the present prospective study, the postoperative outcome was similar to literature as ten patients (16%) developed postoperative pancreatic fistula, mainly in grade B patients (5 patients) and less in grade C patients (2 patients). Most patients followed distal pancreatectomy (8 cases), while only two cases with a severe fistula (graded as grade C) followed pancreatico-duodenectomy. The low fistula rate following pancreaticoduodenectomy is related to the anastomotic technique between the pancreatic duct and the mucosa

of the jejunum. Concerning grade B fistulas, radiological drainage of the discharge was a routine practice in all cases. The drain was kept in situ for three weeks, and all patients improved. Grade C required surgical re-intervention and refashioning of the pancreatico-jejunostomy. One patient got better, while the other got grade C fistula again and died four weeks later—four months after the first surgery. We found that most fistulas developed after MCN and SPPN resection, as most of these cases underwent distal pancreatectomy.

A study performed by Stefano A. et al. stated that independent predictors of postoperative pancreatic fistula were body mass index, operative time, and acute postoperative pancreatitis. (20). However, the univariate analysis of our study added that symptomatic disease ($p = 0.006$) and the location of the disease at the tail of the pancreas ($p = 0.02$) (RR 3.15, 95%CI 1.51-6.73) are risk factors of pancreatic fistula. Furthermore, our study did not evaluate the texture of the pancreas or the body mass index and its relationship with the postoperative fistula.

In the present study, recurrence occurred in 6 patients (9.5%), and most recurrent cases occurred at the resection margin (four patients), mainly after mucinous cystic neoplasm surgery. Recurrence was diagnosed based on CT, MRI, and biopsy.

Several studies concerning MCN surgery analyzed the variation of the recurrence rates in accordance with the benign or malignant nature of the lesion. Reddy et al. reported a retrospective study on 56 patients diagnosed with MCN. In that study, 50 patients (89%) had an adenoma, and no recurrence was noted after surgery in these benign cases (21). On the other hand, Ohtsuka et al. recently reported that after four years of follow-up, eight patients with malignant resection had a distant metastasis at the liver but no recurrence at the site of resection (22). In our study, evidence of post-operative benign MCN was found in 73.6% of the cases, and malignant MCN was found in 26.4%. The high incidence of malignant MCN could explain the high incidence of recurrence after MCN resection. Furthermore, recurrence occurred mostly at the resection margin. At six, ten, and 12 months, MCN recurrences were documented. Two patients denied redo surgery and preferred chemotherapy, while a third patient underwent a redo operation. The index operation of the malignant MCN recurrence that underwent surgery was distal pancreatectomy without splenectomy, and the redo operation was an open resection of the recurrent tumour with splenectomy due to malignant infiltration. The recurrence involved the descending colon with subsequent left hemi-colectomy with colo-colic anastomosis by stapplers (23). Intraoperative frozen section pathology was done to ensure a negative resection margin. Redo-operation is an effective intervention in small cases.

Several studies also dealt with the recurrence after resection of IPMNs; Chari et al. stated in their study on IPMN surgery that recurrence after resection of invasive IPMN was observed in 26 of 40 (65%) patients, and it was mainly at the resection margin. Sixty-four percent of the patients had distant metastasis to the liver, and overall, 91% of the cases recurred within three years after resection (24). On the contrary, a study reported a lower recurrence of 5–10% after resectioning IPMNs and an initial negative resection margin in 8% of these patients (25). Concerning recurrent cases after IPMN resection, a study by White R et al. suggested that if recurrence occurs, the patient may still benefit from a redo resection (26). In this study, one patient (1/9, 11.1%) had a recurrence of IPMN after resection. The recurrence happened at the resection margin and was found seven months after the surgery. The recurrent patient of IPMN underwent reoperation due to evidence of malignant recurrence. The index operation was pylorus-preserving pancreatectomy, and the redo operation was a total pancreatectomy without preservation of the pylorus. Redo-operation is an effective intervention in small cases. In this case, low pressure pneumoperitoneum was done during redo surgery as the patient had cardiopulmonary risk (27).

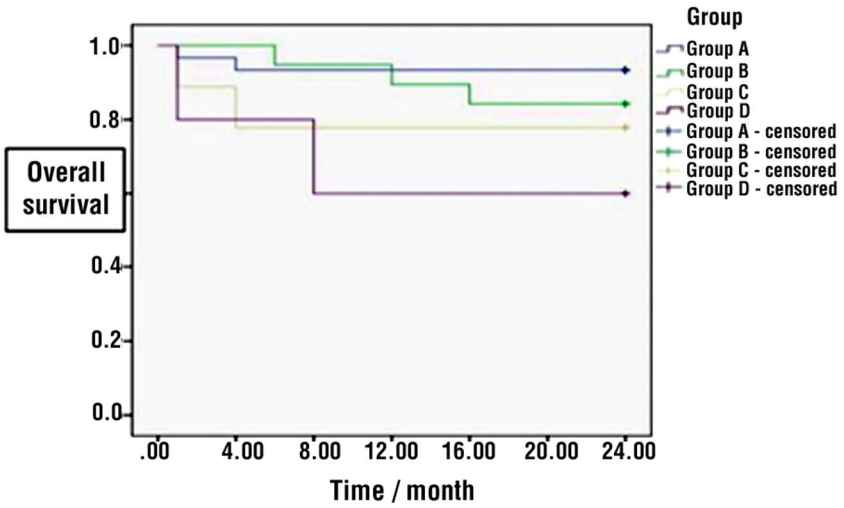
SCNs are considered benign entities. However, three cases were diagnosed preoperatively with EUS/FNAC as malignant; however; the postoperative histopathological exam showed that only one was malignant SCN, which recurred in the eighth month. The index operation for the recurrent case of SCN was pylorus-preserving pancreaticoduodenectomy. The redo operation was total pancreatectomy without pylorus-preserving and closing the pancreatic-jejunal anastomosis.

The last case of recurrence concerned SPT malignant neoplasm. An SPT recurrence patient was detected during the seventh postoperative month. The index operation was distal pancreatectomy without splenectomy, and the redo operation was resection of the recurrent tumor with splenectomy due to malignant infiltration.

Symptomatic disease, location at the head, elevated CA19-9, and pancreatic duct <5mm were significantly associated with recurrence.

Intraoperative frozen section pathology was done to ensure a negative resection margin. All specimens were exposed to pathological examination by the same

Figure 2 - Kaplan-Meier analysis of overall survival of patients of the studied 4 groups



pathologist that confirmed the recurrence of the tumor. All cases that refused redo surgery underwent a full course of chemotherapy. Our study's overall survival for MCN (84.2%) and IPMN (88.9%) was higher than the average in the literature. This promising outcome can be explained by a short follow-up period. However, overall survival for SPPT (80%) was lower than in previous evidence (*fig. 2*).

Our study evaluates the surgical resection of PCNs and the major postoperative complications, such as pancreatic fistula and recurrence of the tumor. This study assessed the importance of redoing surgery for recurrent cases after the preoperative confirmation of resectability.

A limitation of our study is the moderate sample size. This could be explained by the fact that PCNs are not very common and by the criteria of eligibility for surgery. We included cases of a confirmed diagnosis of true exocrine pancreatic cystic neoplasms that were proved preoperative or postoperative. However, this study did not determine the predictive value of malignancy in these tumors. Furthermore, our study did not evaluate the texture of the pancreas or the body mass index and its relationship with postoperative recurrence or fistula. Another limitation was the short follow-up period.

CONCLUSION

Our results concur that surgical resections of these tumors, either open or laparoscopic, are safe and feasible. The most common complication was a pancreatic fistula (ten cases, 16%), six recurrences (9.5%), and a satisfactory overall survival rate of 90.4% at 2.5 years. Our findings follow the European Expert Consensus Statement on Pancreatic Cystic Neoplasms released in 2018.

Conflict of interests and funding: none.

Ethics approval, consent to participate

Medical Ethical Committee of Zagazig University gave us all the ethical agreements. The study was registered at https://clinicaltrials.gov/ NCT04747600. The study was reported according to the STROBE guidelines.

The study followed the World Medical Association's Code of Ethics (Helsinki Declaration) for human experiments.

Availability of data and materials

Will be available on demand.

Authors' contributions

Study design: TAAMH,AR, A K , AI, AA, AAR, WA.A. Data collection: T.A.A.M.H,AR,W.P.C, A K ,AI, S.E.S, WA.A, AS,AAR .Diagnosis of patients by endoscopic ultrasound and postoperative adjuvant therapy: RH, SES,AAR, MRK, AB Statistical analysis: MME, Data interpretation: TAAMH, AR, AK, AI, AA, MME, WA.A. Literature search: TAAMH, AR, MME, WAM. Manuscript writing: All authors. Final approval of manuscript: All authors.

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